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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/40, 31/445, 31/55

A1

(11) International Publication Number: WO 91/19495

(43) International Publication Date: 26 December 1991 (26.12.91)

(21) International Application Number: PCT/JP91/00768

(22) International Filing Date: 7 June 1991 (07.06.91)

(30) Priority data:

9012942.0	11 June 1990 (11.06.90)	GB
9012951.1	11 June 1990 (11.06.90)	GB
9012952.9	11 June 1990 (11.06.90)	GB
9012953.7	11 June 1990 (11.06.90)	GB
9012954.5	11 June 1990 (11.06.90)	GB
9012955.2	11 June 1990 (11.06.90)	GB
9012956.0	11 June 1990 (11.06.90)	GB
9012957.8	11 June 1990 (11.06.90)	GB
9012958.6	11 June 1990 (11.06.90)	GB
9012959.4	11 June 1990 (11.06.90)	GB
9012960.2	11 June 1990 (11.06.90)	GB
9012961.0	11 June 1990 (11.06.90)	GB
9017701.5	13 August 1990 (13.08.90)	GB

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: USE OF A MACROLIDE COMPOUND SUCH AS FK 506 FOR MANUFACTURING A MEDICAMENT FOR TREATING IDIOPATHIC THROMBOCYTOPENIC PURPURA AND BASEDOW'S DISEASE

(57) Abstract

Macrolide compounds such as the FR-900506 and its related compounds are provided for the prevention or treatment of idiopathic thrombocytopenic purpura and Basedow's disease. Composition containing such compounds is also disclosed.

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DESCRIPTION

USE OF A MACROLIDE COMPOUND SUCH AS FK 506 FOR MANUFACTURING A MEDICAMENT FOR TREATING IDIOPATHIC THROMBOCYTOPENIC PURPURA AND BASEDOW'S DISEASE

This invention relates to a new use of macrolide compounds for idiopathic thrombocytopenic purpura and Basedow's disease.

Accordingly, this invention provides a new use of the macrolide compounds for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease.

Further, this invention provides a prophylactic or therapeutic agent for idiopathic thrombocytopenic purpura and Basedow's disease, which comprises the macrolide compounds.

Still further, this invention provides a method for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease, which comprises administering said macrolide compounds to mammals.

The macrolide compounds used in this invention are known and disclosed, for example, in European Patent Publication No. 0184162 and International Publication No. WO 89/05304.

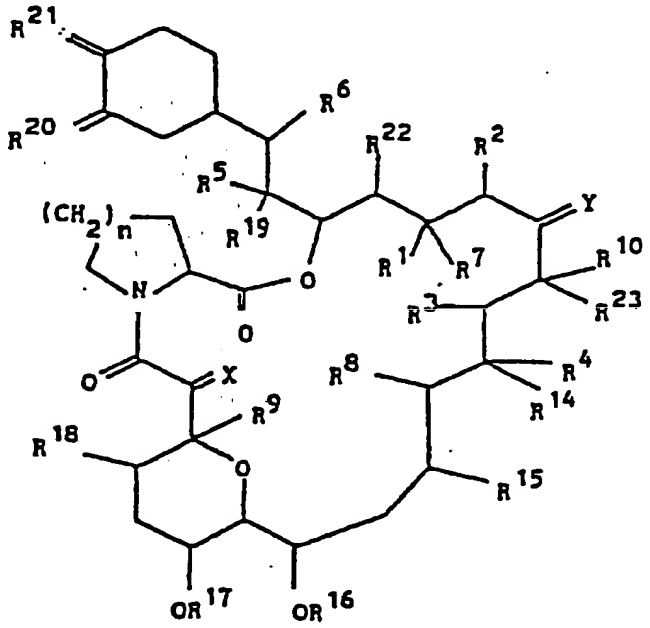
Those known macrolide compounds include the fermentation products, such as FR-900506, FR-900520, FR-900523 and FR-900525, isolated from microorganisms belonging to genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 (FERM BP-927) or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 (FERM BP-928), and their related compounds prepared from these fermentation products.

These macrolide compounds were indicated inter alia for use in the treatment of rejection to transplantation, autoimmune diseases and infectious diseases.

The inventors of this invention have surprisingly found

that the macrolide compounds mentioned hereinbelow are useful for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease.

The macrolide compounds used in this invention can be represented by the following general formula (I).



I

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 and R^9 independently represent H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or

more hydroxyl groups, or alkyl substituted by =O;

X represents O, (H,OH), (H,H) or $-CH_2O-$;

Y represents O, (H,OH), (H,H), N-$NR^{11}R^{12}$ or N-OR^{13};

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

R^{20} and R^{21} independently represent O, or they may independently represent ($R^{20}a$,H) and ($R^{21}a$,H) respectively;

$R^{20}a$ and $R^{21}a$ independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or $R^{21}a$ is protected hydroxy;

in addition, $R^{20}a$ and $R^{21}a$ may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O-containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$.

The specific examples of the definitions of compound (I) and the preferred working modes of the invention are described in detail below.

The term " lower " as used in this specification means, unless otherwise indicated, any number of carbon atoms between 1 and 6, inclusive.

Suitable " alkyl " means straight or branched saturated aliphatic hydrocarbon residue and may include lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, and the like.

Suitable " alkenyl " means straight or branched unsaturated aliphatic hydrocarbon residue having one double bond and may include lower alkenyl such as vinyl, propenyl, butenyl, methylpropenyl, pentenyl, hexenyl, and the like.

Suitable " aryl " may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like.

Suitable examples of the protective group in the " protected hydroxyl group " may include:
1-(lower alkylthio)(lower)alkyl groups such as lower alkylthiomethyl groups (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more desirably C_1-C_4 alkylthiomethyl groups, and most desirably methylthiomethyl;
tri-substituted silyl groups such as tri(lower)-alkylsilyl groups (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl-dimethylsilyl, tri-tert-butylsilyl, etc.);
lower alkyl-diarylsilyl groups (e.g. methyldiphenyl-silyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyl-diphenylsilyl, etc.), more desirably tri(C_1-C_4)alkylsilyl and C_1-C_4 alkyldiphenylsilyl groups and most desirably tert-butyldimethylsilyl and tert-butyldiphenylsilyl; and
acyl groups such as aliphatic acyl groups, aromatic acyl groups and aliphatic acyl groups substituted by aromatic groups, which are derived from carboxylic acids, sulfonic acids or carbamic acids.

The aliphatic acyl group may includes lower alkanoyl groups which may optionally have one or more suitable substituents such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkoxy-(lower)alkanoyl groups which may optionally have one or more appropriate substituents such as lower alkyl (e.g.

cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl groups having one or more suitable substituents such as carboxy or protected carboxy, for example carboxy(lower)alkylcarbamoyl groups(e.g. carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), protected carboxy(lower)alkylcarbamoyl groups such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl groups(e.g. trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropyl carbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

The aromatic acyl group may include aroyl groups which may optionally have one or more suitable substituents such as nitro (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc), arenesulfonyl groups which may optionally have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), and so on.

The aromatic group-substituted aliphatic acyl group may include ar(lower)alkanoyl groups which may optionally have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and so on.

Among the above-mentioned acyl groups, the more desirable acyl groups are C_1-C_4 alkanoyl groups which may optionally be substituted by carboxy, cyclo(C_5-C_6)alkyloxy-(C_1-C_4)alkanoyl groups having two (C_1-C_4)alkyl groups in the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1-C_4)alkyl-carbamoyl groups, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl-(C_1-C_4)alkylcarbamoyl groups, benzoyl which may have one or two nitro groups, halogen-substituted benzenesulfonyl groups, phenyl(C_1-C_4)alkanoyl groups having C_1-C_4 alkoxy and trihalo(C_1-C_4)alkyl groups. Of these groups, the most desirable are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Suitable " 5- or 6-membered N-, S- or O-containing heterocyclic ring " may include pyrrolyl, tetrahydrofuryl, and the like.

Preferred embodiments of the Symbols R^1 to R^{10}, R^{14} to R^{23}, X, Y and n are as follows.

R^1 and R^2 are each hydrogen or combined to form a second bond;

R^3 and R^4 are combined to form a second bond;

R^5 and R^6 are combined to form a second bond;

R^7 is hydrogen, hydroxy, O-lower alkyl such as methoxy or protected hydroxy;

R^8 is hydrogen;

R^9 is hydroxy;

R^{10} is methyl, ethyl, propyl or allyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are each methyl;

R^{20} is oxo or [R^{20}a,H], wherein R^{20}a is hydroxy or methoxy;

R^{21} is [R^{21}a,H], wherein R^{21}a is hydroxy or protected hydroxy;

R^{23} is hydrogen;

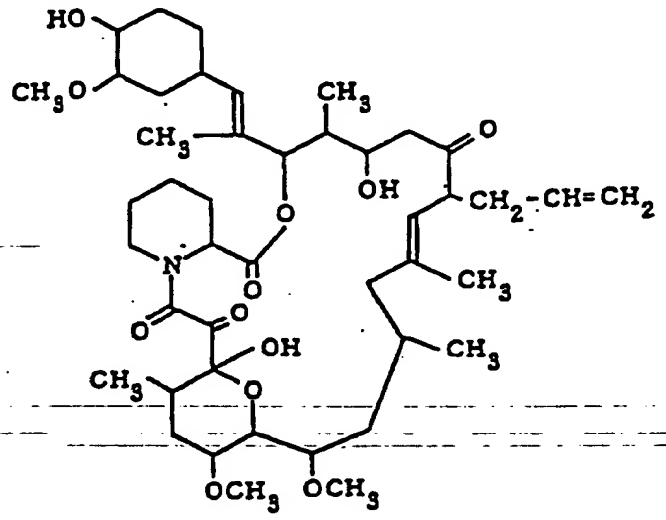
X is oxo, (H,OH) or (H,H);

Y is oxo; and
n is 1 or 2.

The pharmaceutically acceptable salt of the compound (I) is a nontoxic salt, which may be the corresponding salt with an inorganic or organic base such as alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), ammonium salt and amine salts (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and so on.

Referring to compound (I), there may exist conformers or one pair or more of stereoisomers such as optical and geometrical isomers due to the asymmetric carbon or the double bond. Such conformers and isomers also fall within the scope of the invention.

Particularly, the most interesting compound is FR-900506 of the following formula.



(hereinafter, described as FK506)

The macrolid compounds of the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the macrolide compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by oral, parenteral, external, enteral, intravenous, or intramuscular administration.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon

the ag and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.3 mg/kg/day.

Further, the macrolide compounds (I) used in the present invention are also useful for treating or preventing renal diseases selected from interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy;
nervous diseases selected from multiple myositis, Guillain-Barré syndrome, Ménière's disease and radiculopathy;
endocrine diseases selected from hyperthyroidism;
hematic diseases selected from pure red cell aplasia, aplastic anemia, hypoplastic anemia, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia;
bone diseases such as osteoporosis;
respiratory diseases selected from sarcoidosis, fibroid lung and idiopathic interstitial pneumonia;
eye diseases selected from herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukmas, ocular pemphigus, Mooren's ulcer, scleritis and Grave's ophthalmopathy;
skin diseases selected from dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma;
circulatory diseases selected from arteriosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis;
collagen diseases selected from scleroderma, Wegener's granuloma and Sjogren's syndrome;
adiposis;

eosinophilic fasciitis;
periodontal dis ase;
muscular dystrophy; and so on.

And further, it is considered that the compounds described in the European Patent Publication Nos. 0349049, 0349061, 0358508, 0364031, 0364032, 0378317, 0378320, 037321, 0388153, 0396399, 0396400, 0399579, 0403242, 0356399, 0402931, 0353678; British Patent Publication No. 2225576; International Patent Application Nos. PCT/GB90/01262 and PCT/JP91/00314; Japanese Patent Application No. 3-53588 (1991), and so on, are also useful for the diseases shown in the present specification.

The following examples are given for the purpose of illustrating the present invention.

Example 1

FK 506	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid

dispersion composition of FK 506 (5 g) (hereinafter, described as SDF). This composition was capsulat d by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 per each capsule.

Example 2

	1mg-Capsule	5mg-Capsule
SDF	5 mg	25 mg
Lactose	59.15 mg	113.6 mg
Magnesium stearate	0.65 mg	1.4 mg

The above-mentioned compounds were capsulated by a conventional manner to provide 1mg- or 5mg-Capsules respectively, in which SDF was prepared in a similar manner to that of Example 1.

Example 3

(1) The solid dispersion composition containing the following compounds were prepared in a similar manner to that of Example 1.

FK 506	10.0 mg
Hydroxypropyl methylcellulose 2910 (TC-5R)	10.0 mg
Lactose	19.75 mg
Croscarmellose sodium (Ac-Di-Sol)	10.0 mg

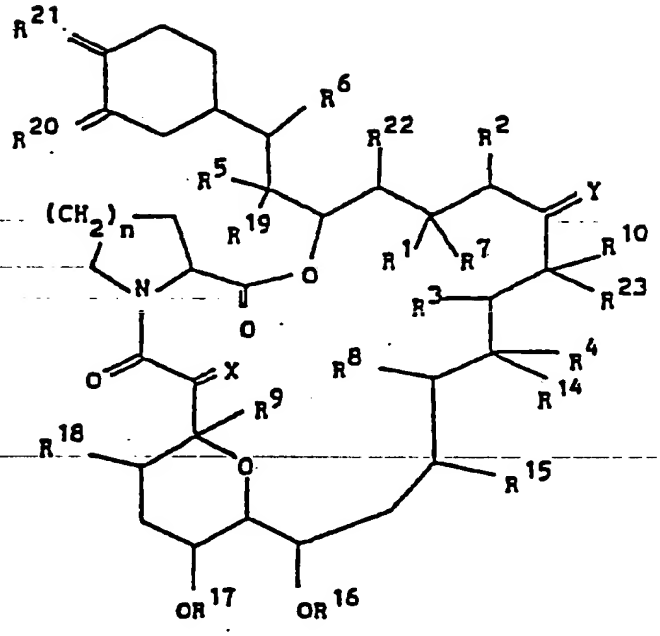
And a tablet was prepared in a conventional manner by using the solid dispersion composition (49.75 mg) mentioned above and magnesium stearate (0.25 mg).

(2) The tablet prepared in (1) was coated with the composition containing the following compounds in a conventional manner.

Titanium oxide	0.85 mg
Hydroxypropyl methylcellulose 2910 (TC-5R)	1.90 mg
Macrogol 6000	0.25 mg

CLAIMS

1. A us of macrolid compounds of the formula:



I

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 and R^9 independently represent H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

X represents O, (H,OH), (H,H) or $-CH_2O-$;

Y represents O, (H,OH), (H,H), $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

R^{20} and R^{21} independently represent O, or they may independently represent ($R^{20}a$,H) and ($R^{21}a$,H) respectively; $R^{20}a$ and $R^{21}a$ independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or $R^{21}a$ is protected hydroxy;

in addition, $R^{20}a$ and $R^{21}a$ may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6-membered N-, S- or O- containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$;

or a pharmaceutically acceptable salt thereof, for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease.

2. A use of the macrolide compounds (I) defined in Claim 1 as a prophylactic or therapeutic agent for idiopathic thrombocytopenic purpura and Basedow's disease.

3. A prophylactic or therapeutic agent for idiopathic thrombocytopenic purpura and Basedow's disease, which comprises the macrolide compounds (I) defined in Claim 1.

4. A method for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease, which comprises administering the macrolide compounds (I) defined in claim 1 to mammals.

5. A use of the macrolide compounds (I) defined in claim 1 for manufacturing a medicament for preventing or treating idiopathic thrombocytopenic purpura and Basedow's disease.

6. A pharmaceutical composition for idiopathic thrombocytopenic purpura and Basedow's disease, which comprises the macrolide compounds (I) defined in Claim 1 in admixture with a carrier or excipient.

7. A process for preparing the pharmaceutical composition of Claim 6, which is characterized by admixing the macrolide compounds (I) with a carrier or excipient.

8. The macrolide compound used in Claims 1 to 7 is FK 506.

INTERNATIONAL SEARCH REPORT

International Applic. No PCT/JP 91/00768

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/40 A 61 K 31/445 A 61 K 31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	KLINISCHE WOCHENSCHRIFT, vol. 68, (suppl. XXI):III, 1990, (Pathophysiology and Pharmacotherapy of Autoimmune Diseases, Satellite Symposium, 29 July 1989), Springer-Verlag, D.B.J. HERRMANN et al.: "Drugs in autoimmune diseases", pages 15-25, see the whole article, in particular page 17 ---	3,5-8
X	WO,A,9004398 (BENDTZEN) 3 May 1990, see the abstract; table 1; page 31, lines 1-10; page 34, lines 16-24; page 37, lines 6-11 ---	3,5-8
X	EP,A,0184162 (FUJISAWA PHARMACEUTICAL) 11 June 1986, see the abstract; page 2, line 16 - page 4, line 16; claims (cited in the application)	3,6-8
Y	--- -/-	5

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10-09-1991	17. 10. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme. M. van der Putt

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0323042 (FISONS) 5 July 1989, see the abstract; page 7, lines 14-22; claims (cited in the application)	3,6-8
Y	EP,A,0323042	5
Y	"The Merck Manual", 15 edition, 1987, pages 1038-1043, Merck & Co., Inc., Rahway, NJ, US, see pages 1038-1043,1159-1160	5
X	IMMUNOLOGY TODAY, vol. 10, no. 1, January 1989, A.W. THOMSON: "FK-506 - How much potential?", pages 1-32, see the whole article	3,6,8
A		5
X	IMMUNOLOGY, vol. 69, no. 2, February 1990, K. YAMAMOTO et al.: "Experimental treatment of autoimmune MRL-lpr/lpr mice with immunosuppressive compound FK506", pages 222-227, see the whole article	3,6,8
A		5
A	CURRENT OPINION IN IMMUNOLOGY, vol. 2, no. 6, 1990, Current Biology Ltd, St.J. COLLIER: "Immunosuppressive drugs", pages 854-858, see the whole article	5

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 1,2,4 because they relate to subject matter not required to be searched by this Authority, namely:

see PCT Rule 39.1(iv)

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a)

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9100768 SA 48953

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9004398	03-05-90	CA-A- 2001790	28-04-90
EP-A- 0184162	11-06-86	AU-B- 592067	04-01-90
		AU-A- 5059685	12-06-86
		JP-A- 3072483	27-03-91
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		JP-A- 61148181	05-07-86
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		EP-A- 0346427	20-12-89
		WO-A- 8905304	15-06-89
		JP-T- 2502463	09-08-90

EPO FORM P0479